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Adjusting Lung Cancer Risks for Temporal and Spatial Variations in Radon Concentration in Dwellings in Gansu Province, China

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Our recent study in Gansu Province, China reported an increasing risk of lung cancer with increasing residential radon concentration that was consistent with previous pooled analyses and with meta-analyses of other residential studies (Wang *et al., Am. J. Epidemiol.* 155, 554–564, 2002). Dosimetry used current radon measurements (1-year track-etch detectors) in homes to characterize concentrations for the previous 30 years, resulting in uncertainties in exposure and possibly reduced estimates of disease risk. We conducted a 3-year substudy in 55 houses to model the temporal and spatial variability in radon levels and to adjust estimates of radon risk. Temporal variation represented the single largest source of uncertainty, suggesting the usefulness of multi-year measurements to assess this variation; however, substantial residual variation remained unexplained. The uncertainty adjustment increased estimates of the excess odds ratio by 50–100%, suggesting that residential radon studies using similar dosimetry may also underestimate radon effects. These results have important implications for risk assessment. © 2005 by Radiation Research Society

INTRODUCTION

Inhalation of radon and its decay products is known to increase the risk of lung cancer (*1–3*). Meta-analyses of published epidemiological studies (*4–6*) and pooled analyses of epidemiological studies in North America[2] (*7*) and in China (*8*) reveal a statistically significant excess risk of lung cancer in long-term residents of homes with high radon levels, consistent with the downward extrapolation from studies of radon-exposed miners.

Precise estimation of risk from residential studies is constrained by uncertainties in radon dosimetry, which requires the characterization of radon levels many years in the past (*9, 10*). Uncertainties arise from the use of current measurements of radon in air to reflect past levels, which may differ due to modified living patterns of occupants, structural alterations, or normal yearly random variation. Uncertainties arise from gaps in the historical record due to homes that are no longer residences or no longer exist, that are located outside the study area, that were occupied briefly and not measured, or that were unmeasured due to refusal of the current occupant. Inadequate characterization of time in the home and movement within the home also increases uncertainty (*11–13*).

Investigators have addressed uncertainties by explicitly adjusting risk estimates under various models (*6, 14, 15*), conducting sensitivity analyses (*16*), limiting participants to long-term residents (*12, 17*), and analytically modeling radon levels for gaps in residential history (*18*). Investigators have also used an improved dosimeter to measure residual radiation embedded in glass artifacts from radon in air and to serve as a cumulative measure of exposure (*19–21*).

We recently reported an increasing lung cancer risk with radon concentration in an epidemiological study in Gansu Province in northwestern China, and we indicated that results could be underestimated by 50–100% due to dosimetric uncertainties (*22*). The effect of uncertainties was based on data from a 3-year measurement substudy to estimate the temporal and spatial variation in radon levels. This report presents analyses of those data and describes the methodology used to adjust the case–control risk estimates.

MATERIALS AND METHODS

Study Area

The case–control study and the measurement substudy were conducted in the predominantly rural prefectures of Pingliang and Qingyang in Gan-

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[2] Krewski *et al.*, Risk of lung cancer in North America associated with residential radon. Manuscript submitted for publication.

su Province, where a large proportion of the population live in a unique style of underground dwelling, *yao-dong* in Chinese, literally "cave dwelling" (*22*). The underground dwellings are generally constructed around a courtyard, with each room consisting of a tunnel 5–12 m in length (*23, 24*).

There are several design categories, depending on position of the dwelling relative to ground level and type of construction. *Underground cave dwellings* have an entrance/courtyard entirely below ground level. *Open-cut cave dwellings* have rooms tunneled into the side of a hill and an entrance/courtyard partially below ground level or fronted by a berm. *Ground cave dwellings* are built into the side of a hill with an unobstructed entrance/courtyard. *Above-ground cave dwellings* are surface dwellings with thick walls and an interior room design of high cylindrical ceilings that mimic underground dwellings. *Standard above-ground dwellings* are built in a more typical style, with one or two levels, a ridged roof, and rectangular rooms. Above-ground cave dwellings generally have more windows than the true underground types but fewer windows than standard above-ground dwellings. People also live in multi-level apartments, generally having not more than six stories.

Underground dwellings were more prevalent historically. Since the 1970s, many families have moved to above-ground homes. In our study, nearly all subjects have lived in an underground dwelling, with 44% of subjects currently living in an underground dwelling.

Case–Control Study: Design and Radon Dosimetry

The case–control study enrolled all lung cancer cases aged 30–75 years diagnosed between January 1994 and April 1998 and resident in the two prefectures (*22*). Controls were randomly sampled from 1990 census lists and frequency matched on age in 1995, sex and prefecture to an expected distribution of cases, derived from a 1991 search of medical records. The study enrolled 886 cases (656 males and 230 females) and 1,765 controls (1,310 males and 455 females).

Interviewers placed two 1-year α-particle track detectors (Track-etch; TechOps-Landauer, Glenwood, IL), one in the living area and one in the sleeping area, in all homes occupied for 2 or more years within a 25-year exposure-time window from 5 to 30 years prior to enrollment. Exposure in this period is thought to influence lung cancer risk most directly (*2*).

We placed 6,703 detectors in homes of subjects (881 of 886 cases and 1,761 of 1,765 controls), along with 742 co-located quality control detectors. We measured 1.3 residences per case and 1.2 residences per control. We calculated the time-weighted average radon concentration within the exposure-time window in becquerels per cubic meter (Bq/m^3), using years of residence as weights. We imputed values for gaps in residential histories using the mean radon concentration of controls' houses within housing type and prefecture, a method shown to be approximately unbiased (*25*). If housing type was not available from the questionnaire, for example, the type was unknown or the house was occupied for less than 2 years, we used the mean radon concentration for all controls within the prefecture. Valid radon data within the exposure-time window were available for 768 cases and 1,659 controls, and covered 71.8 and 79.1% of the exposure-time window, respectively. We also presented results for 463 cases and 1,143 controls with 70% or more coverage of the exposure-time window, where coverage was 96.9% for cases and 98.6% for controls.

Radon Measurement Substudy

A measurement substudy was conducted in Zhenyuan County in Qingyang Prefecture. Although unknown at the time, these houses had some of the highest radon levels in our study. Starting in 1996, we placed six 1-year radon detectors in several rooms (two each at the front, middle and back) of a house for 3 consecutive years. We refer to detectors by the year placed. For example, "1996 detectors" were placed July 1996 and retrieved July 1997, at which time "1997 detectors" were placed. The substudy included 55 houses, 11 houses of each design type, excluding apartments. We placed 1,654 detectors in one to five rooms of each house (mean, 2.3 rooms/house).

Statistical Methods and the Measurement Error Model

For the risk analysis, we fit a linear odds ratio (OR) model: OR(x) = $1 + \beta x$, where x is time-weighted average radon concentration and β is the excess OR (EOR) per Bq/m^3, adjusting for age, prefecture, sex, smoking risk, and socioeconomic status, using standard methodology (*26*).

Three sources of uncertainty were identified: (1) measurement error of the detector, (2) use of contemporary measurements to estimate radon throughout the house and in prior years, and (3) gaps from missing measurements (*6*). Detector errors were small and were ignored. For comparison, we analyzed subjects with 70% or more coverage of the exposure-time window to minimize the third source of error.

We assume that the radon concentration within a dwelling was independent of year, except for random variation, and that changes in the dwelling or pattern of behavior have not influenced radon levels. We assume that radon for a subject's home is unrelated to a previous type of dwelling. For example, although people have tended to move from underground dwellings to standard above-ground dwellings, we assume that the radon level in a standard above-ground dwelling does not depend on whether the subject always lived in the house or moved into the house from an underground dwelling, another standard above-ground dwelling, or an apartment.

The use of current measurements to estimate historical radon concentrations results in observed time-weighted average radon exposures with greater variability than true time-weighted average radon levels and the induction of classical error, which tends to bias risk estimates toward the null[3] (*6, 14*). The use of mean radon concentration from control houses to impute missing data induces Berkson error; i.e., an individual's true exposure deviates randomly from the observed exposure.

For each subject, suppose X_{ij} is the true, but unobserved, radon concentration in the ith house of design type j within the exposure-time window, p_{ij} is the proportion of years in the ith house, and Z_{ij} is the radon measurement. We assume that the number of the houses and the p_{ij}'s are fixed. A subject's true radon exposure is 25 times $\Sigma_{ij}p_{ij}X_{ij}$, and the observed exposure is 25 times $\Sigma_{ij}p_{ij}Z_{ij}$. We assume that X_{ij} are independent, $\log(X_{ij})$ is normally distributed with mean μ_j and variance σ_j^2, U_{ij} is a multiplicative random error independent of X_{ij}, and $\log(U_{ij})$ is normally distributed with mean 0 and variance τ^2. Then $Z_{ij} = X_{ij} \times U_{ij}$ is lognormally distributed with parameters μ_j and $\sigma_j^2 + \tau^2$. Detectors from control houses in the full study provide estimates of μ_j and $\sigma_j^2 + \tau^2$, while the radon substudy provides an estimate of τ^2. The error model specifies random variation about a true mean for each dwelling type and random variation common to all homes. While we cannot verify common uncertainty for different dwellings in the full study, this assumption is supported by the substudy data.

Because lung cancer is a (relatively) rare disease, we use a modified regression calibration approach (*27*). Let X represent $\Sigma_{ij}p_{ij}X_{ij}$, Z represent $\Sigma_{ij}p_{ij}Z_{ij}$, and D represent disease status, with $D = 1$ denoting disease and $D = 0$ disease-free. We assume disease probability is linear in the odds ratio for true exposure:

$$P[D = 1|X] = \frac{e^{\alpha}(1 + \beta X)}{1 + e^{\alpha}(1 + \beta X)}.$$

The goal is to estimate β using observed Z's. We rewrite the model as

$$P[D = 1|Z] = E[D|Z] = E[E(D|X)|Z] = E\left[\frac{e^{\alpha}(1 + \beta X)}{1 + e^{\alpha}(1 + \beta X)}\middle| Z\right]$$

$$\approx \frac{e^{\alpha}(1 + \beta E[X|Z])}{1 + e^{\alpha}(1 + \beta E[X|Z])}$$

The second equation follows from the assumption that Z provides no

[3] Schafer and Gilbert, Statistical ramifications of dose uncertainty in radiation dose–response analyses. Manuscript submitted for publication.

information on disease outcome if true X is known. The approximation should be good if the probability of disease is fairly small, so that the probability of disease is approximately linear in X. Regression calibration replaces Z with the expected true X given Z, denoted $E[X|Z]$ (27). Under our assumptions, the true concentration given the observed $X_{ij}|Z_{ij}$ is log-normal with parameters $[\mu_j \tau^2 + \log(Z_{ij})\sigma_j^2]/(\sigma_j^2 + \tau^2)$ and $\sigma_j^2\tau^2/(\sigma_j^2 + \tau^2)$. We replace observed exposure with the expected "true" exposure and then estimate radon risk. Note that the simple insertion of $E[X_{ij}|Z_{ij}]$ for Z_{ij} ignores uncertainty in $X_{ij}|Z_{ij}$ from the estimation of the log-normal parameters and thus underestimates variability.

We use bootstrap sampling (28) to account for the usual sampling variability of the data, the uncertainty in estimating μ_j and $\sigma_j^2 + \tau^2$ from the control data, and the imputation of gaps in the exposure-time window. There is additional uncertainty due to the estimation of τ^2 from the substudy, which we consider with a sensitivity analysis. Our approach follows.

1. Create a bootstrap data set of 2,108 concentrations by drawing with replacement from the 2,108 radon values of control houses, compute logarithms of radon levels, and calculate mean and standard deviation within each dwelling type and prefecture.
2. With estimates of τ^2 from the substudy and of μ_j and $\sigma_j^2 + \tau^2$ from step 1, compute $E[X_{ij}|Z_{ij}]$ for each dwelling.
3. Calculate "true" time-weighted average radon concentrations for each case–control subject from residential histories.
4. Create a bootstrap data set of 2,427 subjects (1,606 subjects for the restricted analysis) by selecting with replacement from the observed case–control data.
5. Derive the maximum likelihood estimate of β.
6. Repeat steps 1–5 1,000 times to obtain an empirical distribution of β estimates. Identify the median as the bootstrap estimate of β, and the 2.5th and 97.5th percentiles as its 95% confidence interval (CI).

All calculations are carried out using the Epicure suite of programs (29).

In step 4, we did not bootstrap within case status. We ignored case status, so numbers of cases and controls varied for each iteration, thus increasing the variability of the risk estimates slightly, to mimic the original study design in which precise numbers of cases and controls were not known in advance.

Estimation of Temporal and Spatial Uncertainty using the Substudy Data

For the 55 houses, we analyzed type of dwelling (five levels), house within type (11 levels), room (five levels: bedroom, kitchen, main living area, storeroom and other), location within room (three levels: back, middle, front), and year of measurement (three levels: 1996, 1997 and 1998). Dwelling type and house were selected by design and were considered fixed factors in analyses. The room, location within room, and year of measurement were considered random effects. For observed radon, Z, we fit the following nested, mixed-effects regression model:

$$\log[Z_{ij}(r, l, y)] = \mu_{ij} + \varepsilon_{ij}(r) + \varepsilon_{ij}(r, l) + \varepsilon_{ij}(r, l, y) + \varepsilon_e$$

where μ_{ij} are fixed effects parameters representing means of the log-radon concentration for the 55 categories of house by type, $\varepsilon_{ij}(r)$, $\varepsilon_{ij}(r, l)$, and $\varepsilon_{ij}(r, l, y)$ represent effects of a randomly selected room within house and type, location within house, type and room, and year of measurement within house, type, room and location, respectively, and ε_e represents residual error. We assume $\varepsilon_{ij}(r)$, $\varepsilon_{ij}(r, l)$, $\varepsilon_{ij}(r, l, y)$ and ε_e are independent and normally distributed with mean 0 and variances τ_r^2, τ_l^2, τ_y^2, and τ_e^2, respectively. Random error ε_e occurs because replicate measurements in the same year and under the same conditions will yield different values, due to differences in devices, processing, airflow, variations of temperature and humidity, and other factors. We use the PROC MIXED procedure in SAS (30) with the restricted maximum likelihood option.

RESULTS

Measurement Substudy Data

We assessed reproducibility using 490 co-located (duplicate) detectors. After a logarithm transformation, the Pearson correlation coefficient for pairs of detector values was 0.88 with $P = 0.40$ for the paired t test. Figure 1 shows coefficients of variation (CV) for the co-located detectors by room location, type of dwelling, and year of measurement as well as the 5% and 1% control levels. The abscissa value is a sequence number from 1 to 55 assigned after CVs were sorted within dwelling type for pairs located in the front of the room in 1996. The CVs indicate good agreement with no unusual patterns or excessive variability, except perhaps for 1997, when pairs exhibited increased differences for all locations. Variability in the 1997 detectors was unrelated to dwelling type, outdoor temperature, or rainfall (not shown).

We placed 1,164 detectors in one to six rooms of each house (mean 2.8 rooms per house) (Table 1). Excluding co-located detectors, there were between 9 and 36 detectors placed in each dwelling, encompassing 152 distinct rooms. We obtained a complete complement of nine measurements (front, middle and back locations for 3 years) for 104 rooms, and at least three measurements in all except three rooms. Due to changes in use, collapse or problems with detectors, we were unable to measure all rooms in all years.

Underground dwellings were 2 to 10 years older than standard above-ground dwellings. All types had similar arithmetic means (AM), geometric means (GM) and geometric standard deviations (GSD) for radon (Table 1). Based on the Kolmogorov-Smirnov test, radon concentrations were consistent with log-normality, both within type of dwelling ($P = 0.94$, 0.91, 0.83, 0.70, 0.96 for underground cave dwellings, open-cut cave dwellings, ground cave dwellings, above-ground cave dwellings, and standard above-ground dwellings, respectively) and for all data combined ($P = 0.72$) (Fig. 2).

For 1996 and 1997 measurements, AM radon concentrations were lowest in the standard above-ground dwellings compared to the underground style of dwellings; however, standard above-ground dwellings recorded the highest AM radon concentrations in 1998 (Table 1 and Fig. 3). Concentrations were lowest in the front portion of rooms, primarily in the underground types of dwellings, and highest in the interior areas of rooms away from the entrance. There were few differences in concentrations between the back and middle areas of rooms.

The regression showed that there was substantial variation in radon levels within housing types, with suggestive evidence of higher levels in the three underground types of dwellings ($P = 0.07$) (Table 2). Measurement variability was greatest from year to year, with residual variation being only slightly smaller. A smaller proportion of variation was due to room-to-room variation. A non-negative variance component for detector location could not be estimated.

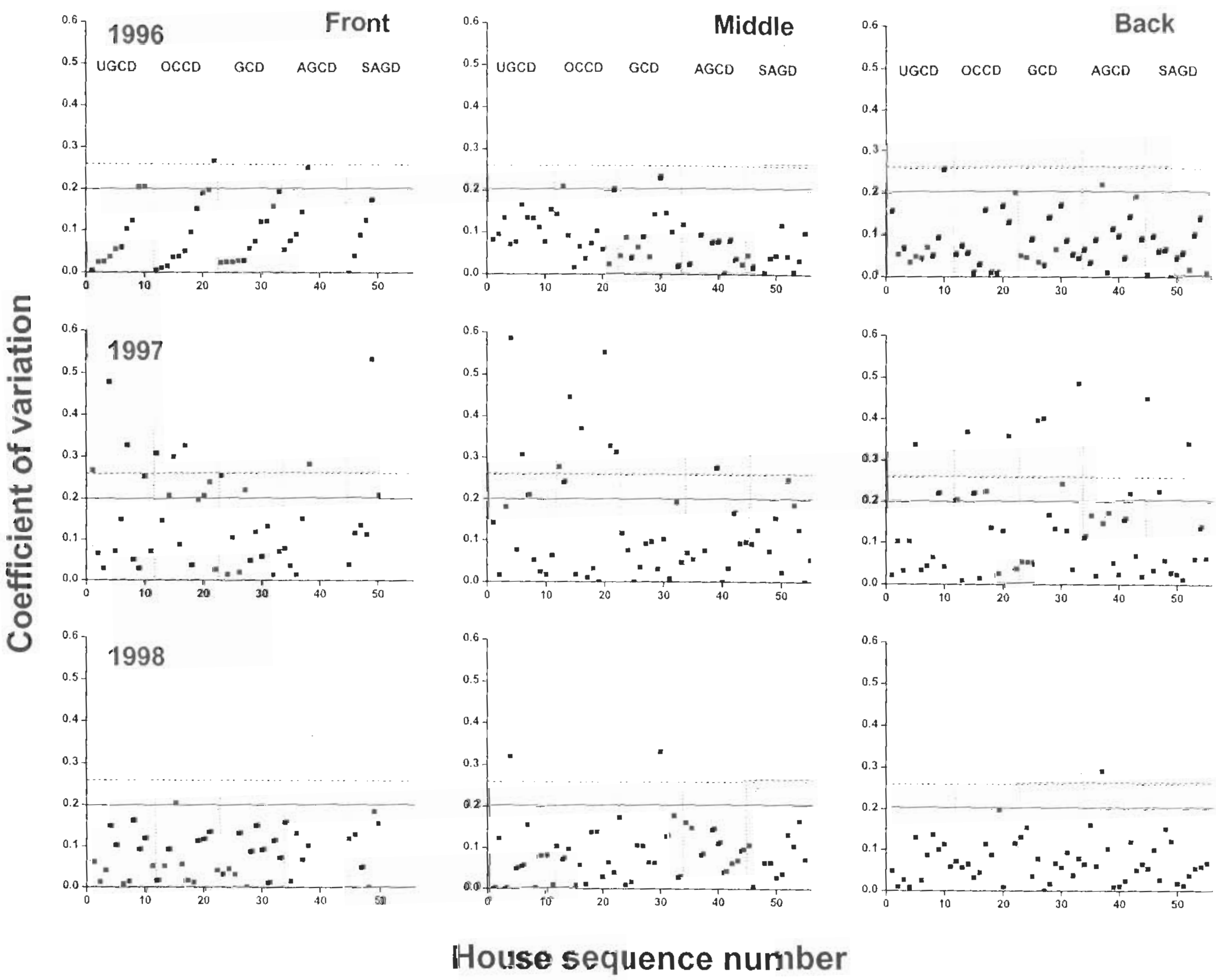

FIG. 1. Coefficients of variation (CV) for co-located detectors by house sequence number for type of dwelling, year of measurement, and location of detector within room. Data from substudy on 55 houses. Solid lines and dashed lines denote 5% (CV = 0.20) and 1% (CV = 0.26) control values. Types of dwellings include underground cave dwelling (underground cave dwellings), open-cut cave dwelling (OCCD), ground cave dwelling (GCD), above-ground cave dwelling (AGCD), and standard above-ground dwelling (SAGD). Sequence number based on ordered CVs for 1996 detectors in the front room location. Year identifies a measurement period from July through June of the next year.

The restricted maximum likelihood estimate of the total variation from sources other than type and dwelling was 0.171 with a standard deviation of 0.011, resulting in an estimated GSD for uncertainties from these factors of $\exp(\tau) = \exp(0.171^{1/2}) \approx 1.50$ with 95% CI (1.47, 1.55).

We fit a regression model to assess the interaction of room, location and year by type of dwelling. Estimates were similar, with the sum of the variance components ranging from a GSD of 1.4 for the above-ground cave dwellings to 1.6 for the standard above-ground dwellings. Values of the Akaike Information Criterion, a measure of model fit, were 1077.6 for the interaction model (with 11 variance parameters) and 1078.8 for the initial model (with three variance parameters), indicating that total temporal and spatial uncertainties were similar across dwelling type.

Uncertainty Adjustment of Odds Ratios in the Case–Control Study

Maximum likelihood estimates of the EOR at 100 Bq/m^3 and likelihood-based 95% confidence intervals (CI) were 0.16 (0.03, 0.40) for the complete data and 0.23 (0.06, 0.57) for the restricted data when uncertainties are not taken into account. The comparable bootstrap estimates were 0.16 (0.02, 0.44) and 0.24 (0.06, 0.62) (Table 3). Our best estimate of uncertainty, $\exp(\tau)$, was 1.50, which resulted in adjusted EOR estimates of 0.29 (0.03, 1.04) for the complete data and 0.65 (0.16, 3.04) for the restricted data, 75% and 170% larger, respectively. EORs at 100 Bq/m^3 for a standard regression calibration approach, ignoring variation of population radon parameters, were similar, 0.29 (0.04, 0.95) and 0.64 (0.17, 2.79), but with narrower CIs. Table 3

TABLE 1
Numbers of Dwellings, Rooms per Dwelling and Rooms Measured per Home, and Mean Radon Concentration in Becquerels per Cubic Meter (Bq/m³) by Year of Measurement, Type of Dwelling, and Location of Detector within a Room

		Underground cave dwelling	Open-cut cave dwelling	Ground cave dwelling	Above-ground cave dwelling	Standard above-ground dwelling	Total
Number of dwellings		11	11	11	11	11	55
Year built		1984.8	1980.2	1976.3[a]	1980.7	1986.7	1981.9[a]
Rooms measured		3.4	2.9	2.5	2.1	3.0	2.8
Residential mean radon (Bq/m³)							
AM[b]		363.6	336.1	389.4	352.5	337.0	355.7
GM		361.5	331.7	380.3	339.6	330.8	348.3
GSD		1.12	1.19	1.25	1.35	1.22	1.23
Radon detector measurements[c] (Bq/m³)							
Year[d]	Location within room						
1996		456.8 (89)	440.6 (84)	476.6 (71)	426.3 (61)	396.7 (80)	439.6
	Front	396.5	376.5	410.5	444.5	375.2	388.7
	Middle	476.7	476.6	506.1	438.6	442.8	465.7
	Back	498.7	468.7	515.1	402.5	375.2	451.2
1997		280.7 (90)	281.1 (84)	306.3 (72)	325.2 (63)	238.5 (81)	284.0
	Front	245.1	231.3	266.4	291.1	212.1	245.2
	Middle	276.9	306.3	319.8	342.9	251.7	297.4
	Back	320.2	305.8	333.3	314.8	237.3	299.9
1998		360.1 (90)	305.8 (85)	347.3 (72)	337.8 (61)	361.8 (81)	342.7
	Front	319.2	272.7	289.2	315.2	327.9	301.4
	Middle	394.1	334.3	373.5	357.2	402.0	373.8
	Back	367.2	310.3	379.3	322.4	332.8	342.2
Total		365.5 (269)	342.4 (253)	376.3 (215)	362.7 (185)	332.1 (242)	

Note. Numbers of radon measurements are shown in parentheses.
[a] Mean excludes one house built in 1890 and one in 1920; means including these houses are 1963.4 for geometric standard deviation type and 1979.0 for all houses.
[b] AM, arithmetic mean; GM, geometric mean; GSD, geometric standard deviation.
[c] AMs of 1,164 detector measurements, excluding co-located detectors.
[d] Year identifies a measurement period from July through June of the next year.

shows adjusted EORs for several exp(τ) values and suggests substantial effects of uncertainty adjustment.

DISCUSSION

The goal of our 3-year measurement substudy in a rural area of China was to characterize the major components of uncertainty in radon dosimetry (i.e. variations of radon levels within rooms, between rooms within dwelling, between dwellings, and over time) so that we could evaluate the effects of this uncertainty in our case–control study of lung cancer. Our analysis suggests that the overall estimate of radon risk found in our lung cancer case–control study, which ignored uncertainty, may have underestimated the true risk by 50 to 100%, depending on the level of uncertainty (*22*). Analysis of the substudy data indicates that the principal source of variation in dosimetry was yearly variation in radon levels, although a substantial amount of variation remained unexplained due to measurement error of the device and other factors, including possible model misspecification. Radon varied little from room to room, as expected, since rooms in underground homes are generally distinct "caves."

Overall estimates of the EOR at 100 Bq/m³ were 0.16 (0.03, 0.40) in the current analysis and 0.19 (0.05, 0.47) in Wang *et al.* (*22*). This difference was due to the imputation procedure for gaps in the exposure-time window. The current analysis used mean radon concentrations for controls by housing type and prefecture (12 values), while the previous analysis used prefecture-specific mean radon (two values). Note that the source of the mean values used for the imputation procedure was misstated in Wang *et al.* (*22*). Missing data were more likely in earlier, and therefore underground, homes, which typically had higher radon levels. This resulted in higher mean radon levels in the current analysis (232.7 Bq/m³ for cases and 226.1 Bq/m³ for controls) than in the previous analysis (230.4 Bq/m³ for cases and 222.2 Bq/m³ for controls) and lower EOR estimates. EORs were the same in the restricted data, since there was little imputation.

Adjustment for uncertainties had a greater impact in the restricted data than in the overall data (Table 3). We eval-

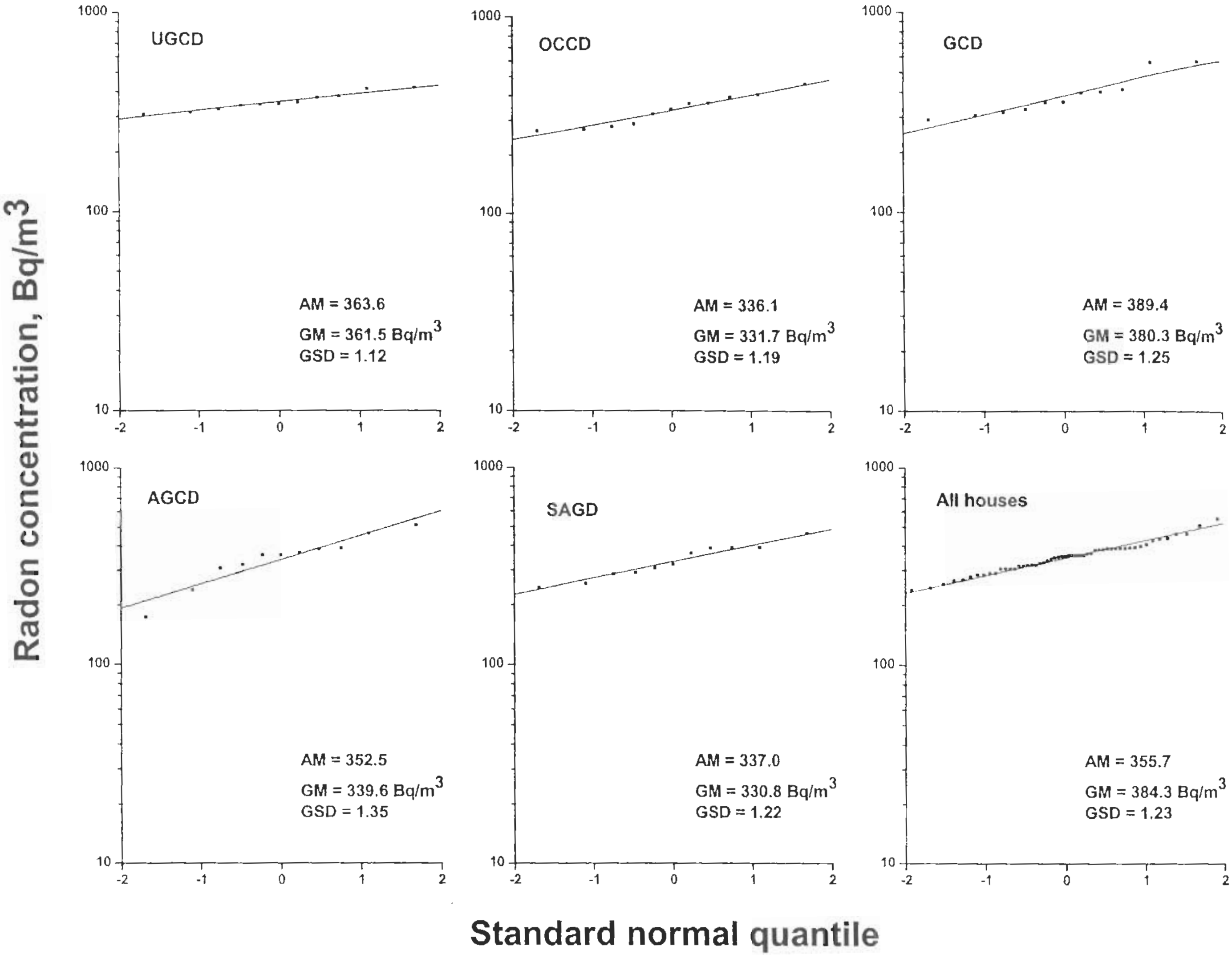

FIG. 2. Quantile plot of mean radon concentration for 55 houses by type of dwelling. Types of dwellings include underground cave dwelling (UGCD), open-cut cave dwelling (OCCD), ground cave dwelling (GCD), above-ground cave dwelling (AGCD), and standard above-ground dwelling (SAGD). Fitted maximum likelihood line, arithmetic mean (AM), geometric mean (GM) and geometric standard deviation (GSD) are shown.

uated several factors to explain this difference, including type of dwelling, coverage, number of residences, imputation method, and the confounding variables, but we were unable to account fully for the greater impact. Regression calibration, i.e. replacing Z with $E[X|Z]$, shrank exposures toward the mean of the true distribution and reduced the range of exposures. Adjusted exposures had about half the standard deviation of the unadjusted exposures. For unadjusted time-weighted average radon concentrations, 10.1 and 18.2% of controls were under 100 Bq/^{3} and at or above 300 Bq/m^3, respectively. For adjusted concentrations with GSD = 1.50, 3.1% and 7.8% of controls were in these categories. The corresponding percentages in controls with 70% or greater coverage were 14.2 and 20.6% for the unadjusted concentrations and 4.4 and 10.1% for adjusted concentrations. Differences thus appeared to result from the reduced variability of the adjusted exposures, particularly in the restricted data.

Underground dwellings in Gansu are unique, even within China, and the extent to which these results apply to other areas is uncertain. However, temporal variation represented the single largest source of uncertainty, suggesting the usefulness of multi-year measurements to assess this variation. Since temporal variation is unrelated to type of house, it is likely to be important in other residential radon studies as well.

Recent analyses of uncertainties resulted in adjustments which increased risk estimates by 50–100%, similar to our overall results. In a southwest England study, the estimate of the EOR at 100 Bq/m^3 increased after adjustment from 0.08 (−0.03, 0.20) to 0.12 (−0.05, 0.33) for all subjects and from 0.14 (0.01, 0.29) to 0.24 (−0.01, 0.56) for subjects with complete coverage of the exposure-time window (*6*). Using a best CV estimate of 0.55 (or GSD = 1.67) and a range from 0.30 to 0.60 (GSDs from 1.32 to 1.74), EORs in a Swedish study increased from 0.10 to 0.15–0.20

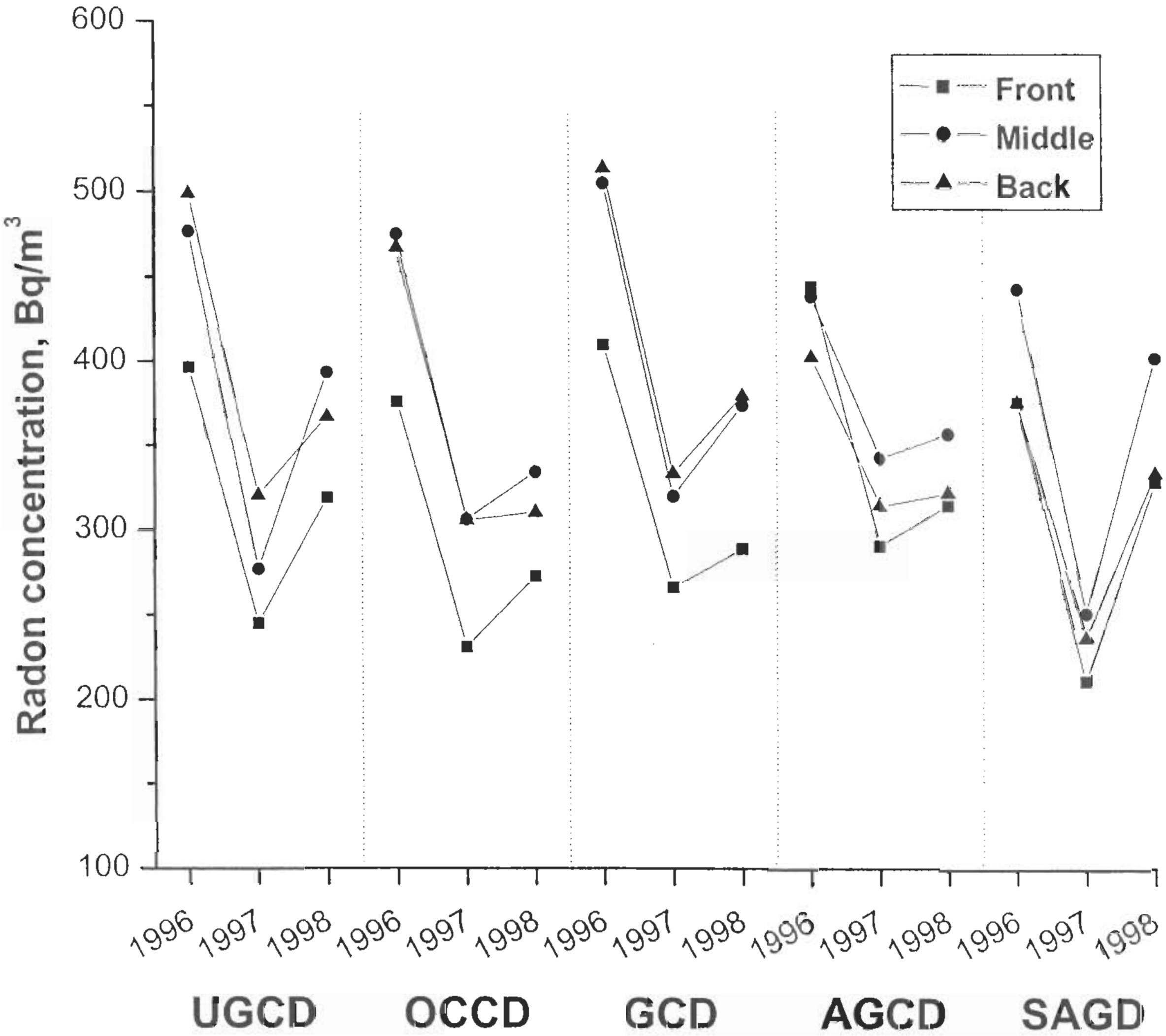

FIG. 3. Arithmetic mean radon concentrations for 1,164 detectors by type of dwelling and year of measurement for detectors located in the front, middle and back of rooms. Types of dwellings include underground cave dwelling (UGCD), open-cut cave dwelling (OCCD), ground cave dwelling (GCD), above-ground cave dwelling (AGCD), and standard above-ground dwelling (SAGD).

(*16*). Our estimate of uncertainties was GSD = 1.50, corresponding to a CV of 0.43 with 95% CI of (0.40, 0.46), and in the low range of values used in the Swedish analysis (*16*). Our lower GSD may be due to greater homogeneity in dwellings in Gansu and the use of 3-month detectors in the Swedish study.

An alternative approach to addressing temporal uncertainty measures cumulative exposure directly. A study of Missouri women used CR-39 surface measurement devices and reported an EOR of 0.63 (95% CI: 0.1, 1.9) at 100 Bq/m^3 but found no excess risk with dosimetry based on standard 1-year air radon detectors (*19*). Surface detectors measure emissions from polonium-210, a decay product of radon-222, embedded in glass artifacts, such as picture glass and mirrors, that may reflect historical exposure better than contemporary air measurements (*21*). A Swedish study estimated an EOR at 100 Bq/m^3 of 0.33 (−0.12, 2.0) with dosimetry based on air radon measurements and 0.75 (−0.04, 4.30) based on surface monitors (*20*). Surface monitors may offer an improved measurement technology, but they do not eliminate temporal uncertainties, due to misspecification of age of the artifact and the exact location of the artifact over time, or address spatial uncertainties from within house variation.

Another alternative for reducing uncertainties is through study design. An Iowa study enrolled only long-term (20 years or more) residents, thereby minimizing uncertainties from residential mobility (*12*). The exposure assessment also included measurements throughout the house, adjustment for residential occupancy, and time spent in other buildings and outdoors (*31*). The EORs at 100 Bq/m^3 were among the highest observed to date and ranged from 0.16 (0.0, 0.6) for all subjects to 0.33 (0.02, 1.23) for living subjects. A study in Finland also restricted participants to current residents of 20 years or more duration and estimated an EOR at 100 Bq/m^3 of 0.11 (0.09, 1.3) (*17*).

We did not address all components of uncertainty. We ignored exposures more than 30 years prior, which may

TABLE 2
Results from the Mixed-Effects Regression Analysis of the Natural Logarithm of Radon Concentration on Type of Dwelling, House, Room within House, Location of Detector, and Year of Measurement (1996–1998)

Source	Nested factors		
		Fixed effects[a]	
		df	*F* value (*P*)
Type		4	2.2 (0.07)
House	Type	50	1.6 (0.01)
		Random effects[b]	
		Estimate	SD
Room	Type, house	0.0330	0.0096
Location	Room, type, house	—	—
Year	Location, room, type, house	0.0705	0.0075
Residual		0.0674	0.0053
Total		0.1709	0.0110

Note. Data include 1,164 detector measurements.
[a] For fixed effects, analysis of variance results include degrees of freedom (*df*), the *F* statistic, and its *P* value of significance.
[b] Restricted maximum likelihood estimate of the variance component and its standard deviation (SD). "—" indicates a positive variance estimate could not be estimated.

have an impact, albeit small, on lung cancer risk (*2*). However, exposure assessment becomes increasingly problematic for exposures far in the past. We also did not account for outdoor radon exposures. In a separate air pollution study in 25 houses conducted in April 1995, we measured outdoor radon adjacent to one residence using grab sampling (*32, 33*). For one 24-h period, outdoor radon averaged 35.4 Bq/m³ and ranged from 3.1 Bq/m³ at 18:33 h to 93.9 Bq/m³ at 09:03 h. The 24-h indoor radon concentration of an adjacent house was 235.9 Bq/m³. Our outdoor measurement was similar to the AM of 22.2 Bq/m³ with a maximum of 105.4 Bq/m³ found in outdoor areas of Gansu from a 1984–1990 national survey using grab samples (*34*). If outdoor radon exposures were the same for cases and controls, then ignoring those exposures would reduce the observed exposure–response estimate (*35*).

We have no data on long-term radon trends. While there was significant heterogeneity in radon over the 3-year period of the substudy, there was no discernible pattern. We found no relationship between yearly radon means and monthly mean temperature or rainfall for the 3 years, year of house construction, or lifestyle characteristics of the residents.

In summary, we found a statistically significant exposure–response relationship in our case–control study of radon and lung cancer in Gansu, China. Based on the evaluation of the uncertainties in assessing radon exposure within the exposure-time window, an adjustment for uncertainties increased our estimate of the excess risk by 50–100%.

TABLE 3
Estimate of Excess Odds Ratio[a] (EOR) at 100 Bq/m³ Based on Bootstrap Simulations, Accounting for the Geometric Standard Deviation (GSD) of Dosimetry Error

GSD of error	All data		≥70% coverage of the exposure time window[c]	
	$\beta \times 100$	95% CI[b]	$\beta \times 100$	95% CI[b]
1.00[d]	0.164	(0.02, 0.44)	0.240	(0.06, 0.62)
1.40	0.258	(0.03, 0.79)	0.483	(0.13, 1.62)
1.50	0.287	(0.03, 1.04)	0.650	(0.16, 3.04)
1.60	0.329	(0.02, 1.35)	0.960	(0.23, 7.32)

[a] Model includes adjustment for referent age, sex, ownership of a color television, number of cattle, smoking risk, and prefecture, with the odds ratio linear in radon concentration, $OR(x) = 1 + \beta x$.
[b] CI, confidence interval.
[c] Data restricted to subjects with 70% or more of the 5–30-year exposure time window covered by radon measurements.
[d] Maximum likelihood estimates of β at 100 Bq/m³ and 95% likelihood-based CI based on observed exposure data were 0.160 (0.03, 0.40) for all data and 0.233 (0.06, 0.57) for the restricted data.

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